

## Supernumerary Chromosome Marker Der(22)t(11;22) Resulting from a Maternal Balanced Translocation

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Derivative 22 [der(22)] syndrome is a rare disorder associated with multiple congenital anomalies including pre-auricular skin tags or pits, conotruncal heart defects, and profound mental retardation. Der(22)t(11;22) is one of the causes of supernumerary chromosome markers (mar) in humans. We present a boy with developmental delay and multiple anomalies consistent with the supernumerary der(22) syndrome. Cytogenetic analysis showed an abnormal chromosome complement of 47, XY, +mar in all 50 cells analyzed. The karyotype of his mother showed a reciprocal translocation over the distal bands 11q23 and 22q11, respectively, i.e., 46,XX,t(11;22)(q23.3;q11.2), and that of his father was 46,XY. Thus, the nature of the supernumerary chromosome markers was of der(22)t(11;22)(q23.3;q11.2). The clinical features, including craniofacial dysmorphism, hypotonia, psychomotor retardation, heart defects, and urogenital anomalies, were the combined effects of partial trisomies for both distal 11q and pericentromeric 22q. (*Chang Gung Med J* 2003;26:48-52)

**Key words:** der(22), t(11;22), supernumerary marker, partial trisomy 11, partial trisomy 22.

A reciprocal translocation between chromosomes 11 and 22 is a site-specific translocation that has been seen in many family members with no common ancestry.<sup>(1)</sup> This translocation is of particular interest because male and female balanced carriers have a 0.7 % and 3.7% risk of having children with the supernumerary der(22), respectively.<sup>(2)</sup> The t(11;22)(q23;q11) translocation is also the most frequently identified familial reciprocal translocation in humans.<sup>(1,3)</sup> The unbalanced offspring of such translocation carriers usually present with supernumerary derivatives of chromosome 22, i.e., der(22)t(11;22). The supernumerary der(22)t(11;22) syndrome is characterized by mental deficiency, malformed ears with pre-auricular pits or tags, high-arched or cleft palates, micrognathia, and congenital heart defects.<sup>(3)</sup> The reported neurological abnormalities have also included microcephaly, delayed psy-

chomotor development, and dilated ventricles of brain.<sup>(1-5)</sup> In the translocation carrier, 3:1 meiotic segregation with tertiary trisomy can occur, resulting in abnormal progeny with the der(22) as the supernumerary chromosome markers.<sup>(3-5)</sup> However, this supernumerary marker, especially the de novo form, is often misdiagnosed as chromosome 22 or others.<sup>(5,6)</sup> I present a boy with non-mosaic supernumerary der(22)t(11;22) syndrome resulting from a maternal balanced reciprocal translocation.

### CASE REPORT

My boy patient was the first child of healthy, young parents born at the gestational age of 39 weeks via Cesarean section due to breech presentation and fetal distress. His prenatal life was complicated with oligohydramnios and small kidneys,

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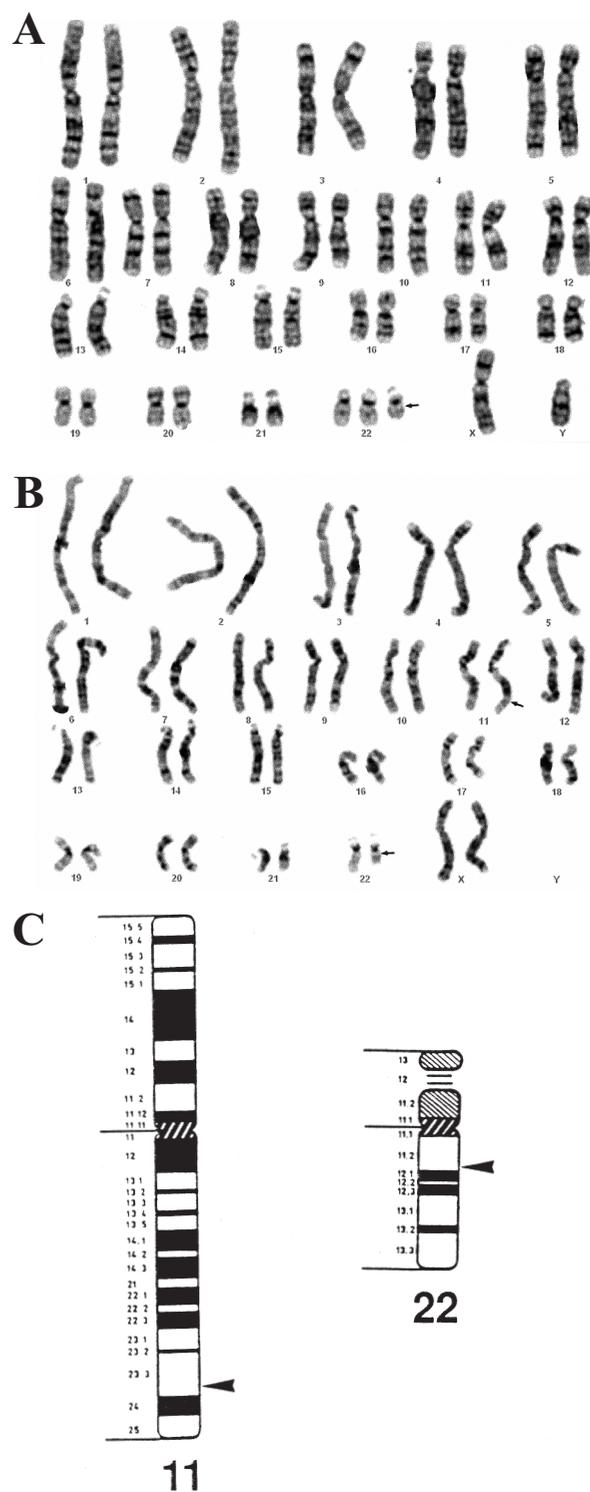
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which were detected on sonography. He was small for his age with head circumference (HC) of 31 cm, body weight (BW) of 2578 g and body height (BH) of 47 cm. Dyspnea, poor feeding, oliguria and cyanosis developed at birth. He was hospitalized due to severe dehydration with acute renal failure at 1 month of age, when postnatal growth retardation was apparent (HC, 32.0 cm; BW, 3200 g; and BH, 49 cm, all below the 3rd percentile). On physical examination, he has microcephaly with frontal bossing, wrinkled forehead, hypopigmented hair and skin, scanty eyebrows and hair, ptosis of the left eye, epicanthal folds, downward slanting palpebral fissures, flat tip to the nose due to a short septum, increased naso-labial distance with a well-formed and prominent philtrum, thick lips, high-arched palate, micrognathia, underdeveloped ears, bilateral preauricular pits (Fig. 1), and bilateral inverted nipples. A grade II/VI systolic murmur over the precordial area was detected. Both little fingers had four phalanges. Cubitus valgus and flexion contraction over the left elbow was noted. In addition to right cryptorchism, bilateral hydrocele and micropenis were found.



**Fig. 1** Face of the patient at 2 years of age. Note the scanty hair, prominent philtrum, thick lips, micrognathia, large auricle with pre-auricular pit.



**Fig. 2** Partial G-banded karyograms of the proband (A) and the mother (B). Arrows indicate the abnormal chromosomes. (C) Ideogram shows the breakpoints (arrowheads).

Thyroid function and electrolytes (calcium, phosphate, sodium and potassium) were normal. The initial renal function was impaired with elevated levels of blood urea nitrogen (from 80 to 58 mg/dL) and creatinine (from 2.4 to 1.4 mg/dL). Ophthalmologic examination revealed hypopigmented fundus, but no coloboma. Echocardiogram showed a patent ductus arteriosus (PDA), a type II atrial septal defect (ASD II), pulmonary valve stenosis with hypoplastic annulus, and an aberrant right subclavian artery. Brain echography showed moderate dilatation of lateral ventricles and hypoplastic corpus callosum. Renal echography showed hypoplastic kidneys with increased echogenicity. Auditory brain stem evoked potential study showed peripheral sensorineural hearing impairment over the left side. A tentative diagnosis of branchio-oto-renal (BOR) syndrome was made. Chromosome study of the patient showed an abnormal karyotype: 47,XY,+mar (Fig. 2A) in all 50 cells analyzed. Further study of his mother showed 46,XX,t(11;22)(q23.3;q11.2) (Fig. 2B) and father 46,XY. The chromosomal complement of the proband was thus 47, XY, +der (22) t(11;22)(q23.3;q11.2) mat. Ligations of the PDA and pulmonary valvulotomy with patch closure of ASD II were performed at the ages of 3 months and 14 months, respectively.

During the following 3 years of follow-up, microcephaly, failure to thrive, short stature, and motor delay persisted despite participation in a rehabilitation program. At 3 years of age, he could not stand, with HC of 45.3 cm (<3rd percentile). At 4 years of age, he had ataxic gait and could only speak simple words. His HC was 46.5 cm (<3rd percentile), weight was 11 kg (<3rd percentile), and height was 92.5 cm (3~10th percentile). Magnetic resonance images of his brain showed plagiocephaly without other structural anomalies. Results of the renal function test and urinalysis were normal.

## DISCUSSION

This patient was noted to have multiple congenital anomalies and developmental delays after birth. Chromosomal study showed an extra chromosome marker of the G-group size. Small supernumerary marker chromosomes have rarely been seen in routine cytogenetic analysis. The patient did not have the phenotype of Down syndrome (trisomy 21).

True complete trisomy 22 was not considered because it is not compatible with life. From the karyotypes of the parents, the nature of the supernumerary marker was delineated as the composition: 22pter-22q11.2:11q23.3-11qter. Identification of the marker chromosomes delineated the clinical effects of specific extra genetic materials on the proband, and helped us to understand how markers form and to perform genetic counseling.<sup>(6)</sup> Reciprocal translocation t(11;22)(q23;q11) is of particular interest because the unbalanced offspring of the translocation carriers usually present with a supernumerary derivative of chromosome 22.

The constitutional t(11;22) translocation is the only known recurrent non-Robertsonian translocation in humans.<sup>(1,3)</sup> Carriers are phenotypically normal and often remain undetected until diagnosis due to infertility or the birth of chromosomally unbalanced offspring. Supernumerary der(22)t(11;22) syndrome can occur in the progeny of balanced t(11;22) carriers, because of malsegregation of the der(22).<sup>(3-5)</sup> Der(22) syndrome patients carry a der(22)t(11;22)(q23;q11) chromosome and are therefore trisomic for 11q23-qter and 22pter-q11. The main features are moderate mental retardation, mild craniofacial anomalies, genital abnormalities, and congenital heart defects.<sup>(1-5)</sup> BOR syndrome should be considered as a differential diagnosis in this patient. BOR syndrome is defined by the presence of at least three of the four following major features: hearing loss, branchial clefts, ear pits, and renal abnormalities.<sup>(7)</sup> It is an autosomal dominant disorder with considerable variability of phenotype within families. Mutations in the EYA1 gene (localized to 8q13.3) have been identified in nearly 70% of BOR syndrome cases.<sup>(7)</sup> Der(22) syndrome may account for some cases with BOR phenotype when mutations undetected.

Maternal transmission of this unbalanced translocation was concluded,<sup>(2,5)</sup> but the underlying mechanisms are not clear. Furthermore, the chromosome 22q11 region was susceptible to rearrangements because this area contains low copy repeats (LCR) sequence block (i.e., the break-prone region 22q11.2). The existence of LCR22S may mediate a number of distinct rearrangements on 22q11 by homologous recombination mechanisms leading to several congenital anomaly disorders.<sup>(1)</sup> They include deletion diseases such as velo-cardio-facial syndrome/DiGeorge anomaly, duplications in cat-eye

syndrome and der(22) syndrome, or genetic disorders such as chronic myelogenous leukemia caused by t(9;22). Most cases occur sporadically in the population, suggesting that this region is prone to chromosome rearrangements.<sup>(1,4,8)</sup> In addition, the formation of a hairpin in palindromic AT-rich sequences flanking both the chromosome 11 and the chromosome 22 breakpoints may generate the t(11;22) translocation.<sup>(8,9)</sup>

The chromosomal region 11q23 may involve CDREL 1 and MLL genes. Balanced carriers may be at increased risk for neoplasia due to the involvement of the genes in tumorigenesis on 11q23. The finding of a significant association between breast cancer and the constitutional translocation t(11;22)(q23;q11) suggests involvement of additional breast cancer gene(s) on 11q23, 22q11, or both. The patients with t(11;22) may be prone to the development of breast cancer.<sup>(10)</sup> However, this translocation does not seem to directly disrupt any active gene or generation of an aberrant fusion gene. A comprehensive array-based analysis of genes located near both translocation breakpoints is a possible way to solve this question.

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## 源於平衡轉位母親之多餘染色體標誌der(22)t(11;22)

侯家瑋

第二十二號染色體衍生物症候群[簡稱der(22)症]是一種罕見的疾病，臨床症狀包括先天多重畸形及重度智障。已知因第十一及第二十二號染色體之間不平衡轉位所形成的der(22)t(11;22)是人類多餘染色體標誌的成因之一。本文報告一典型der(22)症男孩。細胞遺傳學檢查發現多出一個染色體標誌。經由父母親的染色體檢查發現母親為一平衡轉位的帶病者，核型為46, XX, t(11;22)(q23.3;q11.2)，父親則為46, XY。由此可確立此染色體標誌乃源於der(22)t(11;22)(q23.3;q11.2)。病人的表現型，包括臉部特徵、肌肉低張力、精神運動遲緩、先天性心臟病及生殖泌尿道畸形皆是染色體11q末端及22q中心小體周圍多出遺傳物質共同作用的結果。(長庚醫誌 2003;26:48-52)

**關鍵字：**第二十二號染色體衍生物，轉位(11;22)，多餘染色體標誌，11q部分三體症，22q部分三體症。

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